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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/890,006 | 10/25/2001 | Bruce H. Morimoto | 5412/1E887US2 | 4547 |

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Darby & Darby
805 Third Avenue
New York, NY 10022-7513

| EXAMINER | |
|---|---|
| KISHORE, GOLLAMUDI S | |
| **ART UNIT** | **PAPER NUMBER** |
| 1615 | |

DATE MAILED: 04/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/890,006 | MORIMOTO ET AL. | |
| | Examiner | Art Unit | |
| | Gollamudi S. Kishore, Ph.D | 1615 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *03 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-3,8-15,17-20 and 22-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 8-15, 17-20 and 22-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

The amendment dated 1-3-05 is acknowledged.

Claims included in the prosecution are 1-3, 8-15, 17-20 and 22-26.

### *Claim Rejections - 35 USC § 112*

1. Claims 1-3, 8-15, 17-20 and 22-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds wherein phosphocholine is directly linked to steroids, does not reasonably provide enablement for attachment through multitudes claimed linkers and multitudes of moieties defined in X. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d, 1400 (Fed.Cir.1988). Among these factors are: (1) the nature of the invention; 2) the state of the prior art; 3) the relative skill of those in the art; 4) the predictability or unpredictability of the art; 5) the breadth of the claims; 6) the amount of direction or guidance presented; 7) the presence or absence of working examples; and 8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

1) The nature of the invention: the invention concerns with compounds wherein a phosphocholine is attached to a therapeutic compound through various linker units.

2) The state of the prior art: the state of the prior art is very high in terms of attaching therapeutic drugs to phospholipids; however, it is unclear however, whether one could prepare compounds through multitudes of linkers as recited only in claims 1-3 and 9.

3) The relative skill of those in the art: the skill of one of ordinary skill in the art is very high (Ph.D level technology). It should be pointed out preparation of compounds, if they can be prepared takes years of bench work.

4) The predictability or unpredictability in the art: it is unclear whether multitudes of compounds can be prepared at all and if they can be prepared whether they would retain the drug efficacy since it depends on the efficient release from various linker units.

5). The breadth of the claims. The breadth of the claims is very broad in terms of the linker units.

6) The amount of direction of guidance provided: instant specification provides no guidance at all in terms of how various linkers are attached to various drugs claimed. In fact, the specification does not even recite these linkers and the drugs claimed.

7) The presence or absence of working examples: the only working example provided is the attachment of specific steroid with phosphocholine by direct linkage and not through linkers and X moiety.

8) The quantity of experimentation necessary: since instant specification does not provide adequate guidance, it is difficult for one of ordinary skill in the art to choose the proper linker and X moiety and the drug without undue experimentation. Broad claims

must have broad basis of support in the specification; in the absence of such support, claims must be limited to drugs attached directly to the phosphocholine.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant directs the examiner's attention to pages 14 and 15, which according to applicant describes the synthetic routes for preparing the claimed drug X-linker therapeutic agent. A careful review of these pages indicates that the compound prepared has no linker unit at all (see the figure on page 15). With regard to applicant's arguments based on pages 16 and 17, the examiner points out that instant specification has only 15 pages and not 17 pages. Applicant also directs the examiner's attention to pages 4, lines 10 which apparently sets forth the nature of the attachment and page 5, line 1 through page 10 line 1 which apparently define the linkers. The examiner is unable to find the locations where the claimed linkers (i), (ii) and (iii) are described. What is described at this location is the direct linkage between the drug and the phospholipid. The rejection is maintained.

### *Claim Rejections - 35 USC § 103*

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-3, 8-15, 17-20 and 22-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chasalow (5,830, 432)

Chasalow discloses compounds wherein a drug derivatives of phosphocholine and methods of increasing the aqueous solubility of bioactive agent by conjugating them to compounds having phosphocholine moieties. Among the phosphocholines described are hydroxyproline-phosphocholine and tyrosine –phosphocholine. According to Chasalow, any active agent could be used and those include steroids and aspirin (note the abstract, col. 2, line 25 through col. 4, line 65; examples and claims). . Example 5 in particular shows the attachment of DHEA (steroid) through alcohol linkage to phosphohomocholine.

What are lacking in Chasalow are the examples, wherein of the attachment of instant drugs to the phosphate group of phosphocholine through a linker moiety which is an alkanoyl group. However, It would have been obvious to one of ordinary skill in the art to attach the alcohol functional group of the therapeutic agent to phosphocholine derivative having a carboxylic function (linker) and prepare the prodrugs since Chasalow teaches phosphocholine derivatives with compounds such as hydroxyproline, which have carboxylic functional groups. Such is within the skill of the art. Applicant has not shown any unexpected results modifying the basic teachings of Chasalow by indirectly liking DHEA to phosphocholine, which Chasalow has shown through an example (example 5).

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that Chasalow is completely silent with respect to using a

linker wherein the X moiety is attached to the therapeutic agent via an alcohol functional group. This argument is not found to be persuasive since Chasalow as pointed out above teaches not just phosphocholine, but also hydroxyproline derivatives of phosphocholine and based on the guidance provided it would be obvious to one of ordinary skill in the art to link this derivative to the alcohol containing therapeutic drug such as DHEA through the carbonyl function. According to instant claim 2, Y is a heterocyclo (C1-8) alkyl and hydroxyproline is a 5-member ring containing heterocyclo compound.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K. Page can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gollamudi S Kishore, Ph.D
Primary Examiner
Art Unit 1615

GSK